THYROID DYSFUNCTION IN CHRONIC RENAL FAILURE

DISSERTATION SUBMITTED FOR

DOCTOR OF MEDICINE

BRANCH - I (GENERAL MEDICINE)

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CHENNAI

BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"THYROID DYSFUNCTION IN CHRONIC RENAL FAILURE"** submitted by **Dr. C. VASUDEVAN** to the Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of M.D Degree Branch –I (General Medicine) is a bonafide research work were carried out by him under my direct supervision & guidance.

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DECLARATION

I **Dr. C. VASUDEVAN** declare that, I carried out this work on, **"THYROID DYSFUNCTION IN CHRONIC RENAL FAILURE"** at the Department of Medicine, Govt. Rajaji Hospital during the period of August 2008 to October 2009. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, diploma to any other University, Board either in India or abroad.

This is submitted to The Tamilnadu Dr. M. G. R. Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D degree examination in General Medicine.

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INTRODUCTION

"The world is facing a global pandemic of chronic kidney disease. As the morbidity and mortality from infectious diseases decline, life expectancy increases and chronic degenerative diseases have become more prevalent. CKD is unique amongst the chronic non-infectious illnesses…..".[1]

It has been estimated from population survey data that atleast 6% of the adult population in the United States has CKD at stages 1 and 2. An unknown subset of this group will progress to more advanced stages of CKD. An additional 4.5% of the U.S. population is estimated to have stages 3 and 4 CKD. The most frequent cause of CKD is diabetic Nephropathy, most often secondary to Type 2 DM.[2]

India being the diabetic capital of the world, diabetic Nephropathy is the commonest cause of CKD. There are about 7.85 million CKD patients in India.[3]

Patients with End Stage Renal Disease display a variety of endocrine disturbances. However the evidence of endocrine dysfunction commonly consists only of laboratory abnormalities,

many of which are not associated with apparent clinical signs and symptoms of the disease.[4] Among which Thyroid function has been extensively evaluated in patients with CRF.

CRF is a widely recognised cause of nonthyroidal illness causing thyroid dysfunction, ie, alteration in thyroid hormones in the absence of underlying intrinsic thyroid disorder.[5,19]

Chronic renal failure affects thyroid function in multiple ways, including low circulating thyroid hormone concentration, altered peripheral hormone metabolism, disturbed binding to carrier proteins, possible reduction in tissue thyroid content and increased iodine stores in thyroid glands.

TT_3, TT_4, FT_3 are decreased more commonly in patients with CRF. But FT_4, TSH levels are normal in these patients and indicate euthyroid status. We speculate that the low thyroid state in uremia serves to defend against protein wasting and misguided attempts to replete thyroid hormone stores may worsen protein malnutrition.[6]

Some studies showed an increased incidence of subclinical hypothyroidism in CKD patients and higher prevalence of hypothyroidism in patients with terminal renal failure.[7]

It has been estimated that primary hypothyroidism may occur in upto 9.5% of ESRD patients when compared to 0.6 to 1.1% of general population.[7]

When hypothyroidism becomes more severe it can cause reduced cardiac function and lead to progressively worsening kidney function. Thus the prevalence of subclinical hypothyroidism in patients with CKD might be a risk factor for both cardiovascular disease and progressive kidney disease.[8]

This study is designed to determine the prevalence of thyroid dysfunction in CRF patients in order to intervene at an early stage depending upon the hormone abnormalities and reduce both the cardiovascular risk and progressive worsening of kidney function.

REVIEW OF LITERATURE

DEFINITIONS:

1. CKD :

Chronic kidney disease encompasses a spectrum of different pathophysiological processes associated with abnormal kidney function and a progressive decline in GFR.

CKD is classified into five stages according to the guidelines given by National Kidney Foundation (NKF) / (Kidney Dialysis outcome Quality Initiative (KDOQI)).[2]

2. CRF:

Chronic Renal Failure applies to the process of continuing significant irreversible reduction in nephron number and typically corresponds to CKD stages 3 to 5. [2]

3. ESRD:

End Stage Renal Disease represents stage 5 CKD where the accumulation of toxins, fluids and electrolytes results in uremic syndrome.[2]

STAGES OF CRF

Stage	Description	GFR ml/mt per 1.73 m^2
1.	Kidney damage with normal or increased GFR	≥ 90
2.	Kidney damage with mildly decreased GFR	60 - 89
3.	Moderately decreased GFR	30 – 59
4.	Severely decreased GFR	15 – 29
5.	Kidney failure	< 15 or dialysis

Recommended Equations for estimation of GFR using serum creatinine (Pcr), Age, Sex, Race and Body weight.

1. Cockcroft – Gault Equation:

Estimated creatinine clearance (ml/mt)

$$= \frac{(140\text{-Age}) \times \text{body weight in k.g.}}{72 \times \text{Pcr (mg/dl)}}$$

(multiply by 0.85 for women)

2. MDRD Formula : (Modification of Diet in Renal Disease study)

Estimated GFR (ml/mt per 1.73 m^2)

$$= 1.86 \times (Pcr)^{-1.154} \times (Age)^{-0.203}$$

Multiply by 0.742 for women

Multiply by 1.21 for African Americans.

AETIOLOGY OF CRF[1]:

1. Diabetes Mellitus
2. Hypertension
3. Chronic glomerulonephritis
4. Chronic pyelonephritis
5. Hereditary and cystic diseases of Kidney
6. Obstructive uropathy and others.

PREVALENCE OF VARIOUS TYPES OF CKD IN INDIA[9]

S.No.	Aetiology	Indian Population
1.	Diabetes Mellitus	27.4%
2.	Hypertension	15.5%
3.	Glomerulonephritis	19.3%
4.	Interstitial Nephritis	8.6%
5.	Cystic/ Hereditary diseases	3.9%
6.	Miscellaneous	12.1%
7.	Unknown	13.2%
	Total	100%

Source:

Data from the All India CKD registry of the Indian Society of Nephrology.

Clinical Abnormalities in Uremia[2]		
Fluid and electrolyte disturbances	**Neuromuscular disturbances**	**Dermatologic disturbances**
Volume expansion	Fatigue	Pallor
Hyponatremia	Sleep disorders	Hyperpigmentation
Hyperkalemia	Headache	Pruritus
Hyperphosphatemia	Impaired mentation	Ecchymoses
Endocrine-metabolic disturbances	Lethargy	Nephrogenic fibrosing dermopathy
Secondary hyperparathyroidism	Asterixis	Uremic frost
Adynamic bone	Muscular irritability	**Gastrointestinal disturbances**
Vitamin D–deficient osteomalacia	Peripheral neuropathy	Anorexia
Carbohydrate resistance	Restless legs syndrome	Nausea and vomiting
Hyperuricemia	Myoclonus	Gastroenteritis
Hypertriglyceridemia	Seizures	Peptic ulcer
Increased Lp(a) level	Coma	Gastrointestinal bleeding
Decreased high-density lipoprotein level	Muscle cramps	Idiopathic ascites
Protein-energy malnutrition	Myopathy	Peritonitis
Impaired growth and development	**Cardiovascular and pulmonary disturbances**	**Hematologic and immunologic disturbances**
Infertility and sexual dysfunction	Arterial hypertension	Anemia
Amenorrhea	Congestive heart failure or pulmonary edema	Lymphocytopenia
	Pericarditis	Bleeding diathesis
	Hypertrophic or dilated cardiomyopathy	Increased susceptibility to infection
	Uremic lung	Leukopenia
	Accelerated atherosclerosis	Thrombocytopenia

Thyroid hormone secretion, transport and action:

Thyroid gland secretes predominantly thyroxine (T_4) and only a small amount of Triiodothyronine(T_3). Production of T_3 and T_4 in the thyroid is stimulated by Thyroid stimulating hormone (TSH), released from the anterior pituitary in response to stimulation by thyrotropin releasing hormone (TRH), released by hypothalamus. In turn TSH and TRH secretions are inhibited by T4, forming a negative feedback loop that keeps free T_4 level within a narrow range.

Thyroid hormones exist in circulation in both free and bound forms. About 80% of thyroid hormone is bound to thyroxine binding globulin (TBG). TBG has high affinity for thyroid hormones (T_4>T_3). Albumin has relatively low affinity for thyroid hormones and it binds upto 10% of T_4 and 30% T_3. Transthyretin carries about 10% of T4 and little T3. When the effects of various binding proteins are combined, approximately 99.98% of T4 and 99.7% of T_3 are protein bound. But only the unbound form is biologically active and exerts its metabolic actions after binding to nuclear thyroid hormone receptors which have 15 fold higher affinity for T_3 than T_4. So in metabolically active tissues, T_4 is converted into T_3 by deiodinase enzymes.[40]

HYPOTHYROIDISM

DEFINITIONS[10]:

1. HYPOTHYROIDISM:

Syndrome caused by thyroid hormone deficiency.

Primary Hypothyroidism – Primary defect in the thyroid gland to synthesise and secrete thyroid hormones.

Secondary Hypothyroidism – Due to TSH deficiency secondary to disorders of pituitary and hypothalamus.

1. Subclinical Hypothyroidism[28]:

Increased TSH usually <20 mU/L but normal free T_4.

Only minor symptoms are present.

2. Clinical / Overt Hypothyroidism:

Increased TSH usually >20 mU/L and decreaed free T_4.

Prominent signs and symptoms of hypothyroidism are present.

SIGNS AND SYMPTOMS OF HYPOTHYROIDISM [10,28]:

1. Lethargy and tiredness
2. dry skin
3. cold intolerance
4. Hair loss
5. Poor concentration and memory

6. constipation
7. Hoarseness of voice
8. Weight gain with poor appetite
9. Menorrhagia and loss of libido
10. Impaired hearing
11. Myxedema (puffiness of face, hands and feet)
12. Bradycardia
13. Delayed relaxation of tendon reflexes (Pseudo myotonic reflex)

Laboratory Evaluation of Hypothyroidism [40]

A normal TSH level excludes primary (but not secondary) hypothyroidism. If the TSH is elevated, an unbound T_4 level is needed to confirm the presence of clinical hypothyroidism, but T_4 is inferior to TSH when used as a screening test, as it will not detect subclinical hypothyroidism. Circulating unbound T_3 levels are normal in about 25% of patients, reflecting adaptive deiodinase responses to hypothyroidism. T_3 measurements are therefore not indicated.

Once clinical or subclinical hypothyroidism is confirmed, the etiology is usually easily established by demonstrating the presence

of TPO antibodies, which are present in >90% of patients with autoimmune hypothyroidism. TBII can be found in 10–20% of patients, but these determinations are not needed routinely. If there is any doubt about the cause of a goiter associated with hypothyroidism, FNA biopsy can be used to confirm the presence of autoimmune thyroiditis. Other abnormal laboratory findings in hypothyroidism may include increased creatine phosphokinase, elevated cholesterol and triglycerides, and anemia (usually normocytic or macrocytic). Except when accompanied by iron deficiency, the anemia and other abnormalities gradually resolve with thyroxine replacement

Hypothyroidism: Treatment [40]

Clinical Hypothyroidism

If there is no residual thyroid function, the daily replacement dose of levothyroxine is usually 1.6 mcg/kg body weight (typically 100–150 mcg).

Adult patients under 60 without evidence of heart disease may be started on 50–100 mcg levothyroxine (T_4) daily. The dose is adjusted on the basis of TSH levels, with the goal of treatment being a normal TSH, ideally in the lower half of the reference

range. TSH responses are gradual and should be measured about 2 months after instituting treatment or after any subsequent change in levothyroxine dosage. The clinical effects of levothyroxine replacement are often slow to appear. Patients may not experience full relief from symptoms until 3–6 months after normal TSH levels are restored. Adjustment of levothyroxine dosage is made in 12.5- or 25-mcg increments if the TSH is high; decrements of the same magnitude should be made if the TSH is suppressed. Patients with a suppressed TSH of any cause, including T_4 over treatment, have an increased risk of atrial fibrillation and reduced bone density.

There is no place for liothyronine alone as long-term replacement, because the short half-life necessitates three or four daily doses and is associated with fluctuating T_3 levels.

Once full replacement is achieved and TSH levels are stable, follow-up measurement of TSH is recommended at annual intervals and may be extended to every 2–3 years if a normal TSH is maintained over several years. It is important to ensure ongoing adherence, however, as patients do not feel any symptomatic

difference after missing a few doses of levothyroxine, and this sometimes leads to self-discontinuation.

In patients of normal body weight who are taking 200 mcg of levothyroxine per day, an elevated TSH level is often a sign of poor adherence to treatment. T_4 has a long half-life (7 days), patients who miss doses can be advised to take two or three doses of the skipped tablets at once. Other causes of increased levothyroxine requirements must be excluded, particularly malabsorption (e.g., celiac disease, small-bowel surgery), estrogen therapy, and drugs that interfere with T_4 absorption or clearance such as cholestyramine, ferrous sulfate, calcium supplements, lovastatin, aluminum hydroxide, rifampicin, amiodarone, carbamazepine, and phenytoin.

Subclinical Hypothyroidism

By definition, subclinical hypothyroidism refers to biochemical evidence of thyroid hormone deficiency in patients who have few or no apparent clinical features of hypothyroidism. There are no universally accepted recommendations for the management of subclinical hypothyroidism, but the most recently published guidelines do not recommend treatment when TSH levels

are below 10 mU/L. It is important to confirm that any elevation of TSH is sustained over a 3-month period before treatment is given. As long as excessive treatment is avoided, there is no risk in correcting a slightly increased TSH. Moreover, there is a risk that patients will progress to overt hypothyroidism, particularly when the TSH level is elevated and TPO antibodies are present. Treatment is administered by starting with a low dose of levothyroxine (25–50 mcg/d) with the goal of normalizing TSH. If thyroxine is not given, thyroid function should be evaluated annually.

Special Treatment Considerations

Elderly patients may require up to 20% less thyroxine than younger patients. In the elderly, especially patients with known coronary artery disease, the starting dose of levothyroxine is 12.5–25 mcg/d with similar increments every 2–3 months until TSH is normalized. In some patients it may be impossible to achieve full replacement, despite optimal antianginal treatment. *Emergency surgery* is generally safe in patients with untreated hypothyroidism, although routine surgery in a hypothyroid patient should be deferred until euthyroidism is achieved.

Thyroid function should be evaluated immediately after pregnancy is confirmed and at the beginning of the 2nd and 3rd trimesters.The dose of levothyroxine may need to be increased by ≥50% during pregnancy and return to previous levels after delivery. *Myxedema coma* still has a high mortality rate, despite intensive treatment. Clinical manifestations include reduced level of consciousness, sometimes associated with seizures, as well as the other features of hypothyroidism. Hypothermia can reach 23°C (74°F). There may be a history of treated hypothyroidism with poor compliance, or the patient may be previously undiagnosed. Myxedema coma almost always occurs in the elderly and is usually precipitated by factors that impair respiration, such as drugs (especially sedatives, anesthetics, antidepressants), pneumonia, congestive heart failure, myocardial infarction, gastrointestinal bleeding, or cerebrovascular accidents. Sepsis should also be suspected. Exposure to cold may also be a risk factor. Hypoventilation, leading to hypoxia and hypercapnia, plays a major role in pathogenesis; hypoglycemia and dilutional hyponatremia also contribute to the development of myxedema coma.

Levothyroxine can initially be administered as a single intravenous bolus of 500 mcg, which serves as a loading dose. Although further levothyroxine is not strictly necessary for several days, it is usually continued at a dose of 50–100 mcg/d. If suitable intravenous preparation is not available, the same initial dose of levothyroxine can be given by nasogastric tube (though absorption may be impaired in myxedema). An alternative is to give liothyronine (T_3) intravenously or via nasogastric tube, in doses ranging from 10 to 25 mcg every 8–12 h. This treatment has been advocated because T_4 to T_3 conversion is impaired in myxedema coma. However, excess liothyronine has the potential to provoke arrhythmias. Another option is to combine levothyroxine (200 mcg) and liothyronine (25 mcg) as a single, initial intravenous bolus followed by daily treatment with levothyroxine (50–100 mcg/d) and liothyronine (10 mcg every 8 h).

Supportive therapy should be provided to correct any associated metabolic disturbances. External warming is indicated only if the temperature is <30°C, as it can result in cardiovascular collapse . Space blankets should be used to prevent further heat loss. Parenteral hydrocortisone (50 mg every 6 h) should be

administered, as there is impaired adrenal reserve in profound hypothyroidism. Any precipitating factors should be treated, including the early use of broad-spectrum antibiotics, pending the exclusion of infection. Ventilatory support with regular blood gas analysis is usually needed during the first 48 h. Hypertonic saline or intravenous glucose may be needed if there is severe hyponatremia or hypoglycemia; hypotonic intravenous fluids should be avoided because they may exacerbate water retention secondary to reduced renal perfusion and inappropriate vasopressin secretion. The metabolism of most medications is impaired, and sedatives should be avoided if possible or used in reduced doses. Medication blood levels should be monitored, when available, to guide dosage

THYROID DYSFUNCTION IN CRF:

Chronic Renal Failure can cause various endocrine abnormalities, among which thyroid dysfunction is most important one and extensively evaluated by various research workers.

Chronic renal failure affects thyroid function in multiple ways[6].

1. Low circulating thyroid hormone concentration – TT3,TT4,FT3 are reduced[29].

2. Altered peripheral hormone metabolism.
3. disturbed binding to carrier proteins
4. possible reduction in tissue thyroid hormone content.
5. Increased Iodine stores in thyroid glands [35,37].

Low serum T3 is not due to increased T3 degradation or to decreased T_3 secretion from thyroid but is a result of impaired extra thyroidal peripheral conversion of T_4 to T_3.[33]

The reduction in T4 is attributed to the presence of circulating inhibitors (uremic toxins) which impair binding of T_4 to Thyroxine binding globulin (TBG)[12,30].

Despite decreased circulating T_4 and T_3, thyroid stimulating hormone (TSH) level in serum is not elevated. This absence of TSH elevation is not due to dysfunction of hypothalamo-pituitary axis, because truly hypothyroid renal failure patients can mount a high TSH response.[34]

Thyroid hormone losses during Hemodialysis and peritoneal dialysis are trivial and do not require replacement. Serum inorganic iodide and thyroidal iodide content are increased in CRF

patients and thyroid gland enlargement (goitre) is also frequently encountered [6,35,37].

In addition to reduction in TT_3, TT_4, FT_3 levels in serum, some other abnormalities in thyroid hormone metabolism are also reported. These may include elevated bastal TSH values, which may transiently increased to greater than 10mU/L, blunted TSH response to TRH, decreased or absent TSH diurnal rhythm, altered TSH glycosylation and impaired TSH & TRH clearance rates.[11,31,36]

Thus multitude of defects at all levels of hypothalamo-pituitary – thyroido peripheral axis does seem to exist in uremia.[13]

Dialysis therapy minimally affects thyroid hormone metabolism while Zinc, Erythropoietin administration may partially reverse these abnormalities. Thyroid hormone metabolism normalises with renal transplantation.[32]

There have been speculations on the nature of the presumptive inhibitors in uremia patients and drugs have been accounted for low T_3 and T_4 levels[14].

Frusemide and heparin may influence the thyroid hormone levels. Frusemide inhibits T_3,T_4 binding to serum proteins at high levels[16]. Heparin acutely raises both TT_4 & FT_4 levels in blood.[15]

Other drugs known to suppress the thyroid hormone level are glucocorticoids, propranolol, sulphonylurea, phenytoin and phenobarbitone.

Goitre and hypothyroidism may be induced by iodide excess due to reduced renal iodide excretion. [35,37]

CARDIOVASCULAR EFFECTS OF MILD HYPOTHYROIDISM [20,39]

Many patients with CKD have mild reduction in Thyroid function or subclinical hypothyroidism – a condition that becomes more common as kidney function declines, according to a study in the September 2008 issue of clinical journal of the American Society of Nephrology (CJASN).[8]

Patients with CKD are greatly increased risk of cardiovascular disease. Cardiovascular disease remains the most common cause of death in patients with ESRD, and CKD patients are more likely to die from cardiovascular disease than are expected to progress to ESRD. The CKD population has a higher

incidence of traditional cardiovascular risk factors, including diabetes, hypertension and dyslipidemias. In addition overwhelming scientific evidence has shown that decreased GFR and proteinuria are independent risk factors for cardiovascular disease. When sub clinical hypothyroidism coexists, they suffer more decline in cardiac function and progressive kidney disease.

Complications of CKD worsened by coexisting hypothyroidism are,

I. Cardiovascular Complications

- Secondary hypertension
- LV failure and pulmonary edema
- Accelerated atherosclerosis
- Myocardial infarction
- Pericarditis
- Uremic cardiomyopathy

Hypothyroidism is often associated with elevated LDL-c levels due to a reduction in hepatic LDL receptor formation and delayed clearance of LDL.[41]

II. CNS and neuromuscular complications

- Dementia
- Uremic encephalopathy
- Peripheral neuropathy
- Proximal muscle weakness

III. Hematological complications like anemia

Hypothyroidism can cause normocytic normochromic, macrocytic anemia or iron deficiency anemia due to menorrhagia.

IV. Electrolyte imbalance like hyponatremia

Hypothyroidism can cause euvolumic hypoosmolar hyponatremia. The occurrence of hyponatremia with hypothyroidism generally suggests severe disease, including myxedema coma.[42]

V. Fluid overload – edema.

Myxedema may worsen the volume overload state of CRF.

TECHNIQUES USED TO ASSESS THE CARDIOVASCULAR DYSFUNCTION

1. Pulsed tissue Doppler echo
2. Radionuclide Ventriculography
3. Ultrasonic myocardial textural analysis
4. Cardiac MRI

LV DIASTOLIC DYSFUNCTION:

Characterised by

1. Prolonged isovolumetric relaxation time and impaired LV filling. - Due to decreased expression of sarcoplasmic reticulum ATPase or increased expression of phospholamban.

2. Decreased E/A ratio :-

$$= \frac{\text{Early diastolic mitral flow velocity}}{\text{Late diastolic mitral flow velocity}}$$

LV Systolic dysfunction:

1. Increased PEP/ET

   PEP – Preejection period

   ET- Ejection time

2. Precontraction Time and myocardial relaxation time both are prolonged.

3. Changes in the myocardial time intervals in several LV segments are noted.
4. Posterior septum & mitral leaflet annulus are the most affected regions.
5. Preload (EDV) is decreased
6. After load (SVR) is increased

- Due to loss of vasodilatory effects of thyroid hormones.

All these factors cause reduction in cardiac performance.

Abnormal diastolic function may impair coronary flow reserve.

EFFECTS ON VASCULAR SYSTEM:

1. Increased Systemic Vascular Resistance (SVR)
2. Increased arterial stiffness indicated by increased brachial ankle pulse wave velocity
3. Endothelial dysfunction due to impaired Nitric Oxide (NO) availability.
4. All these factors predispose to diastolic HT.

PREVALENCE OF THYROID DYSFUNCTION:

A Major contribution in this field is by Ramirez and associates, who reported upto 58% prevalence of goiter in CRF patients.[16]

Recently, Quoin-verde et al have also reported a higher prevalence of upto 5% of hypothyroidism in patients with terminal renal failure in comparison with that in hospitalised patients with normal renal function(0.6%). [17]

In one study, overall 9.5% of patients with CKD had subclinical hypothyrodism with no abnormal symptoms or signs.

7% of mild CKD patients had low thyroid function when compared to 18% of those with moderate CKD. After adjustment of other factors patients with moderate CKD were 73% more likely to have some thyroid hormone abnormalities[38] in the form of reduction in TT_3, TT_4 or FT_3

Treatment of thyroid dysfunction in CRF:-

Experiments performed to correct the low serum T_3 level by administration of small doses of LT_3 resulted in lesser nitrogen balance and protein degradation. So we speculate that low thyroid state in uremia serves to defend against protein wasting and that

misguided attempts to replete thyroid hormone stores may worsen protein malnutrition.[6]

CKD at all stages constitute a major risk factor for ischemic cardiovascular disease including coronary heart disease because CKD is a state of accelerated atherosclerosis.

Coexisting subclinical/overt hypothyroidism should be treated to reduce the cardiovascular risk and retard the progression of kidney disease.

CKD related risk factors[22] for cardiovascular disease other than secondary HT are

1. Anemia
2. Hyperphosphatemia
3. Hyperparathyroidism.
4. Generalised inflammation (evidenced by increased CRP).
5. Sleep apnea

"Although no recommendations are available regarding the treatment of mild abnormalities of thyroid hormone levels in patients with CKD, these abnormalities could represent a risk factor for cardiovascular disease and might also be implicated in kidney disease progression" comments given by authors Dr.Michel Chonchol of University of Colorado health sciences centre and Dr.Giovanni Targher of University of Verona, Italy.[21]

AIM OF THE STUDY

1. To determine the prevalence of thyroid dysfunction in chronic renal failure patients in stages 3,4 and 5.
2. To correlate the prevalence of thyroid hormone abnormalities with increasing degrees of renal insufficiency.

MATERIALS AND METHODS

Subjects:

Patients admitted in the department of medicine and nephrology who fulfilled the inclusion and exclusion criteria.

Study design:

Cross sectional study.

Ethical committee approval:

Approval was obtained to carry out the study in Govt.Rajaji Hospital, Madurai.

Study setting:

Govt. Rajaji Hospital, Madurai

Study Duration:

August 2008 to October 2009

Study Criteria:

Inclusion Criteria:

Newly detected CRF patients with chronic renal insufficiency defined as

1. An estimated creatinine clearance of < 60 ml/mt.(Stages 3,4&5).
2. USG evidence of chronic renal failure.

Exclusion Criteria:

1) Previously known hypothyroid patients
2) Patients on high dose of frusemide therapy > 100 mg/day.
3) On heparin therapy
4) On steroid therapy
5) On antiepileptics like phenytoin, phenobarbitone
6) On sulphonylureas.
7) On propranolol.

Study Protocol:

Patients admitted in the department of medicine or nephrology in GRH were included in the study according to the criteria after getting informed consent. A well designed proforma was used to collect the demographic and clinical details of the patients.

Limitations of the study:

1. Small sample size. (only 40 patients)
2. Prevalence of hypothyroidism increases as the age advances. So we have to consider the influence of age on hypothyroidism.
3. Geographical variation of goiter and thyroid problems.

Collaborating departments:

1. Dept. of Medicine
2. Dept. of Nephrology
3. Dept. of Endocrinology

Sample collection:

A sample of 40 patients was collected defining the stage 3 to 5 CKD.

Serum creatinine was measured using the modified kinetic jaffe method.

Kidney function was assessed by estimated creatinine clearance which was calculated by using the cockcroft – gault formula

$$= \frac{(140 - \text{Age}) \text{ X Body Weight in kg}}{72 \text{ X Pcr (mg/dl)}}$$

multiply by 0.85 for women.

Thyroid function was assessed by measuring TT_3, TT_4, FT_3, FT_4 and TSH level in serum.

Methods:

1. Blood urea estimation was done by using diacetyl monoxime (DAM) method.

2. Serum creatinine estimation was done by modified kinetic jaffe method.
3. Serum TT_3, TT_4, FT_3 and FT_4 were estimated by competitive chemiluminescent immuno assay.
4. TSH estimation was done by ultra sensitive sandwich chemiluminescent immuno assay.
5. USG abdomen to assess the kidney size and morphology

Statistical Analysis:

The information collected regarding all the selected cases were recorded in the master chart. Data analysis was done with the help of computer using Epidemiological Information Package - 2002 (EPI Info 2002).

Using this software range, frequencies, percentages, means, standard deviations, Chi-square and 'p' values were calculated. Kruskul wallis chi-square test was used to test the significance of difference between quantitative variables and Yate's tests for qualitative variables A 'p' value less than 0.05 is taken to denote significant relationship.

OBSERVATION AND RESULTS

Table -1 : Age Distribution

Age Group (yrs)	Cases	
	Numbers	%
21 – 30	4	10.0
31 – 40	7	17.5
41 – 50	10	25.0
51 – 60	14	35.0
>60	5	12.5
Total	40	100
Range	23 to 75 yrs	
Mean	48.5 yrs	
S.D	12.6 yrs	

Most of the patients in the sample were in the age group of 51-60 years. The range was from 23 to 75 years.

Table 2: Sex

Sex	Cases	
	Numbers	%
Male	30	75
Female	10	25
Total	40	100

Of the 40 patients in the sample 30 patients were males, and 10 patients were females.

Table -3: Diabetes Mellitus

DM	Cases	
	Numbers	%
Yes	11	27.5
No	29	72.5
Total	40	100

Of the 40 patients with CRF, 11 patients (27.5%) were diabetic.

Table -4: Symptoms of Hypothyroidism

Symptoms	Cases	
	Numbers	%
Yes	8	20
No	32	80
Total	40	100

Of the 40 patients with CRF, 8 patients (20%) only were symptomatic and majority (80%) were asymptomatic.

Table -5: Goitre

Goitre	Cases	
	Numbers	%
Yes	7	17.5
No	33	82.5
Total	40	100

Of the 40 patients with CRF, 7 patients (17.5%) had goiter.

Table -6: CRF Stage

CRF STAGE	Cases	
	Numbers	%
3	6	15
4	11	27.5
5	23	57.5
Total	40	100

Of the 40 patients in this sample, 6 patients belonged to stage 3, 11 patients to stage 4 and 23 patients to stage 5.

Table -7: Relationship between CRF Stage and Symptoms of hypothyroidism

CRF STAGE (No.of Pts)	Symptoms			
	YES		NO	
	Number	%	Number	%
3 (6)	-	-	6	10.0
4 (11)	1	9.1	10	90.9
5 (23)	7	30.4	16	69.6

The Table shows that symptoms of hypothyroidism are prominent with advanced stages of renal failure.

Table -8: Thyroid dysfunction

Impression	Cases	
	Numbers	%
Hypothyroidism	3	7.5
Sub clinical hypothyroidism	6	15.0
Some hormone abnormalities	17	42.5
Normal	14	35.0
Total	40	100

Of the 40 patients in this sample,

3 patients (7.5%) had hypothyroidism

6 patients (15%) had subclinical hypothyroidism

17 patients (42.5) had some thyroid hormone abnormalities.

Totally 26 patients (65%) had some thyroid dysfunction.

Table -9: Relationship between CRF Stage & Goitre

CRF STAGE (No.of Pts)	Goitre			
	YES		NO	
	Number	%	Number	%
3(6)	-	-	6	100
4(11)	1	9.1	10	90.9
5(23)	6	26.1	17	73.9

Of the 40 patients in this study group 23 patients had stage 5CKD. The prevalence of goiter was 0% in stage 3 CKD, 9.1% in stage 4 CKD and 26.1% in stage 5 CKD. The higher the stage of CKD, the higher was the prevalence of goiter.

Table -10: Relationship between CRF Stage & thyroid dysfunction

Thyroid Dysfunction	CRF STAGE					
	3		4		5	
	No	%	No	%	No	%
Hypothyroidism	-	-	-	-	3	13
Subclinical Hypothyroidism	-	-	1	9.1	5	21.7
Other hormone abnormalities	1	16.7	6	54.5	10	43.5
Normal	5	83.3	4	36.4	5	21.7
Total	6	100	11	100	23	100

Of the 40 patients in the study group, 23 patients had stage 5 CKD. 13% of stage 5 CKD pts had hypothyroidism when compared to stage 3 (0%) and stage 4(0%). 21.7% of stage 5 CKD patients had sub clinical hypothyroidism when compared to stage 3(0%) and stage 4 (9.1%). Some hormone abnormalities in stages 3,4 &5 CKD were 16.7%, 54.5% and 43.5% respectively. So higher the stage of CKD, higher was the prevalence of thyroid dysfunction. This correlation was found to be statistically significant.

Table -11: Relationship between CRF Stage & hematological parameters and their significance.

Parameter	CRF STAGE						
	3		4		5		'p' value and its significance
	Mean	SD	Mean	SD	Mean	SD	
Blood Sugar	87	9.1	109.9	36.3	96.3	20.6	0.3235 not significant
Blood Urea	75.8	15.2	93.6	11.6	137.4	33.4	0.0001 significant
Serum creatinine	2.13	0.22	3.39	0.26	7.93	2.33	0.0001 significant
TT_3	105.2	16.0	99	43.8	74.4	25.0	0.0375 significant
TT_4	6.19	0.94	5.06	1.1	4.32	1.57	0.0254 significant
FT_3	2.59	0.29	2.1	0.53	1.74	0.54	0.0043 significant
FT_4	1.11	0.21	1.04	0.22	0.91	0.18	0.1148 not significant
TSH	2.08	0.47	3.51	2.05	5.7	3.27	0.0031 significant

Table -12 : Relationship between Thyroid dysfunction and hematological parameters and their significance

Parameter	Thyroid dysfunction								
	Hypothyroidism		Subclinical Thyroidism		Other abnormalities		Normal		'p' value and its significance
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Blood Sugar	107	27.7	90.0	13.9	105.1	32.4	92.9	17.9	0.7649 Not Significant
Blood Urea	136	11.1	125.8	35.0	128.5	43.4	92.6	18	0.0222 Significant
Serum creatinine	9.0	2.55	6.53	2.63	6.64	3.4	3.81	1.61	0.0085 Significant
TT_3	43.0	5.2	85.7	9.2	75.3	35.3	107.7	23	0.0003 Significant
TT_4	1.89	1.07	5.28	0.27	3.96	0.69	6.25	0.86	0.0001 Significant
FT_3	1.23	0.26	2.17	0.49	1.69	0.49	2.37	0.47	0.0001 Significant
FT_4	0.55	0.11	0.9	0.06	0.95	0.15	1.14	0.16	0.0003 Significant
TSH	10.4	0.64	9.62	1.44	3.56	1.45	2.68	0.98	0.0001 Significant

DISCUSSION

Many patients with chronic kidney disease have mild reduction in thyroid function or subclinical hypothyroidism – a condition that becomes more common as kidney function declines(CJASN).[8]

Prevalence of thyroid dysfunction in CRF

According to the article published by the University of Southern California school of medicine, Los angels, USA, overall 9.5% of patients with CKD had subclinical hypothyroidism. 7% of patients with mild CKD had low thyroid function, compared to 18% of those with moderate CKD. After adjustment for other factors, patients with moderate CKD were 73% more likely to have abnormal thyroid function.

Recently, Quion- verde et al have also reported higher prevalence of up to 5% of frank hypothyroidism in patients with chronic renal failure,in comparison with hospitalised patients with normal renal function(0.6%).[18]

In an Indian study, conducted by Dept. of Nephrology, K.E.M Hospital, Mumbai, Maharastra, of 127 patients with CRF

studied,93 patients (73%) showed significant ['p' value (<0.05)] reduction in their TT_3,TT_4,FT_3 levels in serum.[26]

In our study, of the 40 patients studied, 3 pts (7.5%) had hypothyroidism, 6 patients (15%) had subclinical hypothyroidism and 17 patients (42.5%) had some thyroid hormone abnormalities in the form of reduction in TT_3, TT_4 and FT_3 levels. So totally 65% of patients with CKD had thyroid hormone abnormalities.

Prevalence of goitre in CKD

Ramirez and associates, reported upto 58% prevalence of goitre in patients with CKD as compared to 8% in control areas from the same geographic area.[16]

In a study conducted by Victoria sy lim and associates,reported 37% prevalence of goitre.[27]

In our study, of the 40 patients studied, 7 patients (17.5%) had goitre.

Prevalence of symptomatic hypothyroidism in CKD

Most of the CKD patients have low TT3, TT4, FT3 but normal FT4 and TSH levels in serum and they are clinically euthyroid. Some have overt hypothyroidism and even among them many patients are asymptomatic.[4]

In our study, 8 patients 20% were symptomatic and majority – 32 patients (80%) were asymptomatic.

Relationship between CRF stage and thyroid dysfunction:

Higher the stage of CKD, there is an increased prevalence of thyroid dysfunction in CRF patients.

In our study, 13% of stage 5 CKD patients had hypothyroidism when compared to stage 3 (0%) and stage 4 (0%). 21.7% of stage 5 patients had subclinical hypothyroidism when compared to stage 3 (0%) and stage 4(9.1%). Some hormone abnormalities according to stage 3,4&5 CKD were 16.7% 54.5% and 43.5% respectively. Overall the prevalence of thyroid hormone abnormalities in stage 3,4 and 5 CKD pts were 16.7%, 63.6% and 78.2% respectively in our study.

Despite the recent considerable improvements in renal replacement therapy, cardiovascular disease still remains the main cause of morbidity and mortality in CRF patients.[22] It is evident from various studies conducted by Lindner, et al (1974)[23], Stenvinkel, et al (1999)[24], Cheung, et al(2000)[25], and etc.,

So many traditional and nontraditional risk factors are there for cardiovascular disease and its related morbidity and mortality.

Apart from them hypothyroidism and subclinical hypothyrodism are linked to an increased risk of cardiovascular disease and reduced cardiac function.

Patients with CKD are at greatly increased risk of thyroid dysfunction. “Thyroid hormone abnormalities could represent a risk factor for cardiovascular disease and might also be implicated in kidney disease progression” – comments by authors Dr.Michel Chonchol of University of Colorado, Health Sciences Centre and Dr.Giovanni Targher of University of Verona, Italy.[21]

CONCLUSION

- In our study, the overall prevalence of thyroid dysfunction is 65% in patients with chronic kidney disease.
- 7.5% of CKD patients had hypothyroidism.
- 15% had subclinical hypothyrodism.
- 42.5% had some thyroid hormone abnormalities.
- 17.5% of CKD patients had goiter.
- There was a significant correlation between the prevalence of thyroid dysfunction and the stage of chronic kidney disease.
- Higher the degree of renal insufficiency, the higher was the prevalence of thyroid hormone abnormalities.

SUMMARY

The patients with end stage renal disease have multiple alterations of thyroid hormone metabolism in the absence of concurrent thyroid disease. Higher the degree of renal insufficiency, there is an increased incidence of thyroid dysfunction in CRF patients.

In the present study, a sample of 40 patients of CRF, admitted in medical and nephrology wards were assessed for the prevalence of thyroid dysfunction by estimating the thyroid hormones TT_3, TT_4, FT_3, FT_4 and TSH levels in serum. Patients belonged to the age group in the range of 23 to 75 years. 30 were males and 10 were females. Among them 11 patients were diabetic and 29 were non diabetic.

8 patients (20%) had symptoms suggestive of hypothyroidism and 7 patients (17.5%) had goitre on clinical examination.

57.5% of patients belonged to stage 5 CKD. The overall prevalence of thyroid dysfunction was 65%.

Data analysis was done by using the Epidemiological information package 2002.Among the variables studied, Blood urea (P= 0.0222), serum creatinine (p=0.0085). TT_3 (p=0.0375), TT_4

(p=0.0254), FT_3 (p=0.0043) and TSH (p=0.0031) were showed that there was a significant relationship between CRF stage and thyroid dysfunction.

This study did not take into account the factor of dialysis.

This study was designed to determine the prevalence of thyroid dysfunction in CRF patients in order to intervene at an early stage depending upon the hormone abnormalities and reduce both the risk of cardiovascular disease and progression of kidney dysfunction.

TREATMENT OF THYROID DYSFUNCTION IN CRF:

At present, there are no recommendations available regarding the treatment of thyroid hormone abnormalities in CRF patients. low thyroid state (low TT_3, TT_4, FT_3) in uremia serves to defend against protein wasting and that misguided attempts to replete thyroid hormone stores may worsen protein malnutrition in CRF patients.

But at the same time, subclinical and clinical hypothyroidism are associated with increased risk of cardiovascular disease and these conditions need treatment with thyroid hormone.

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ABBREVIATIONS

CKD	:	Chronic Kidney Disease
CRF	:	Chronic Renal Failure
ESRD	:	End Stage Renal Disease
DM	:	Diabetes Mellitus
GFR	:	Glomerular Filtration Rate
Pcr	:	Plasma Creatinine
TT_3	:	Total Triiodothyronine
TT_4	:	Total Thyroxine
FT_3	:	Free Triiodothyronine
FT_4	:	Free Thyroxine
TSH	:	Thyroid Stimulating Hormone
TRH	:	Thyrotropine Releasing Hormone
TBG	:	Thyroid Binding Globulin
EDV	:	End Diastolic Volume
SVR	:	Systemic Vascular Resistance
NO	:	Nitric Oxide
HT	:	Hypertension
LV	:	Left Ventricle
CRP	:	C Reactive Protein
LDL-c	:	Low Density Lipoprotein –cholesterol
NKF	:	National Kidney Foundation
KDOQI	:	Kidney Dialysis Outcome Quality Initiative
TPO	:	Thyroid Peroxidase
TBII	:	TSH binding inhibiting immunoglobulin

MASTER CHART ABBREVIATIONS

M	-	MALE
F	-	FEMALE
Y	-	YES
N	-	NO

NORMAL VALUES OF THYROID HORMONES

TT3	-	60 – 200 ng/dl
TT4	-	4.5 – 12 mcg / dl
FT3	-	1.7 – 4.2 pg / ml
FT4	-	0.7 – 1.8 ng/dl
TSH	-	0.3 – 5.5 micro units / ml

PROFORMA

Name : Age / Sex : Address :
Admitted for : Duration :
Symptoms of Hypothyroidism: Y / N

Past H/o : HT Y/N DM Y/N IHD Y/N

Hypothyroidism Y/N

Personal H/o: Smoking Y/N Alcoholism Y/N

Family H/o : Y/N

General Examination : Consciousness Normal / Abnormal
Anemia + / -
Pedal edema + / -
Dry Skin + / -
Goitre + / -

Vital Signs: PR : BP: RR: T^0 :
U/O:
Weight :

Systemic Examination : CVS : RS:

ABD : CNS:

Investigations:

1. Bl. Hb% 2. Urine : alb 3. Bl : Sugar
TC sug Urea
DC dep Creatinine

4. S.electrolytes : Na^+ 5. ECG
K^+
Cl^-
$HCo3^-$ 6. Xray Chest

7. Echo.:

8. USG abdomen:

9. Thyroid profile: TT3: TT4: FT3: FT4: TSH:

Impression:

Stage of CRF :

MASTER CHART

No.	Age	Sex	DM	SYMPTOMS	Goitre	BS	UREA	CREAT	**TT3**	**TT4**	**FT3**	**FT4**	**TSH**	CRF Stage	Impression
1	55	M	Y	N	N	186	82	2.9	75	3.87	2.19	0.74	3.19	4	TT4 ↓
2	28	M	N	N	N	84	65	2	100	4.99	1.6	0.77	2.8	3	FT3 ↓
3	54	M	N	N	N	78	168	8.4	52	3.9	2.12	0.94	4.81	5	TT3, TT4 ↓
4	38	M	Y	Y	Y	124	134	11.2	40	1.6	1.53	0.53	10.87	5	Hypothyroidism
5	37	F	N	N	N	73	105	2.3	78	5	3.03	1.25	2.01	3	Normal
6	58	F	Y	Y	Y	122	126	6.2	49	3.08	1.05	0.67	9.97	5	Hypothyroidism
7	35	M	N	N	N	80	175	8.6	76	3.82	1.09	0.84	4.93	5	TT4, FT3 ↓
8	48	M	N	N	N	84	72	2.4	108	6.47	2.28	0.93	1.46	3	Normal
9	55	F	N	N	N	97	106	5.5	117	7.01	1.95	0.97	1.19	5	Normal
10	35	M	N	N	N	68	134	4.9	100	5.7	1.93	0.8	8.58	5	Sub Clinical Hypothyroidism
11	70	M	N	Y	N	75	148	9.6	40	1	1.1	0.45	>150	5	Hypothyroidism
12	38	M	N	N	N	86	88	3.4	71	4.7	1.78	0.97	3.89	4	Normal
13	57	M	N	N	N	100	68	2.1	105	6.8	2.41	1.19	1.78	3	Normal
14	55	M	Y	N	N	160	93	3.6	69	4.38	1.72	0.88	0.77	4	TT4 ↓
15	50	M	N	N	N	89	66	1.8	114	6.89	2.38	1.2	2.05	3	Normal
16	33	M	N	N	N	78	198	12.3	45	3.3	1	0.92	1.17	5	TT3, TT4, FT3 ↓
17	50	M	N	N	N	90	98	3.3	192	4.8	1.49	0.74	1.28	4	FT3 ↓
18	65	M	Y	N	N	125	130	6.8	49	2.3	1.8	1.23	4.42	5	TT3, TT4 ↓
19	23	M	N	N	N	85	120	3.8	160	6.8	3.12	1.39	3.96	4	Normal

20	47	M	Y	Y	Y	96	183	10.8	88	5.3	2.12	0.94	12.34	5	Sub Clinical Hypothyroidism
21	53	M	N	N	N	92	79	2.2	126	6.96	2.84	1.3	2.38	3	Normal
22	68	M	N	N	N	89	98	5.2	80	4.96	2.2	1.19	3.06	5	Normal
23	59	M	Y	N	N	118	110	5.9	127	6.88	1.95	0.97	1.89	5	Normal
24	75	M	N	N	N	72	156	7.9	56	3.32	1.55	0.92	4.93	5	TT3, TT4, FT3 ↓
25	25	M	N	N	N	71	92	3.3	102	5.96	2.88	0.93	4.16	4	Normal
26	55	M	N	N	N	97	106	3.5	108	5.32	1.52	1.02	2.8	4	FT3 ↓
27	43	M	N	N	N	85	97	3.7	72	3.8	2.28	1.14	2.35	4	TT4 ↓
28	46	M	Y	N	N	134	120	9	58	4.16	1.48	0.94	3.96	5	TT3, TT4, FT3 ↓
29	58	M	Y	Y	Y	98	144	7.8	82	5.02	3.16	0.89	9.68	5	Sub Clinical Hypothyroidism
30	27	F	N	N	N	102	212	13.4	54	3.82	1.39	0.98	4.88	5	TT3, TT4 ↓
31	58	M	N	N	N	80	117	6.2	98	6.8	2.62	1.2	2.96	5	Normal
32	48	F	Y	N	N	140	78	3.3	120	6.82	1.8	1.32	3.24	4	Normal
33	54	F	N	Y	Y	78	104	6.5	84	4.96	1.93	0.88	8.68	5	Sub Clinical Hypothyroidism
34	62	F	N	N	N	96	98	5.9	102	5.38	1.89	1.08	3.42	5	Normal
35	31	F	N	Y	Y	104	88	3.1	72	5.3	1.92	0.98	8.62	4	Sub Clinical Hypothyroidism
36	56	M	N	N	N	86	170	9.2	56	3.9	1.88	0.9	4.84	5	TT3, TT4 ↓
37	45	M	Y	N	N	136	117	8.1	80	4.1	1.09	0.93	4.46	5	TT4, FT3 ↓
38	44	F	N	Y	Y	96	102	6.1	88	5.4	1.98	0.9	9.82	5	Sub Clinical Hypothyroidism
39	53	F	N	N	N	88	110	6.8	90	3.62	1.12	0.97	4.55	5	TT4, FT3 ↓
40	47	M	N	N	N	105	88	3.4	48	3.92	2.38	1.28	4.4	4	TT3, TT4 ↓

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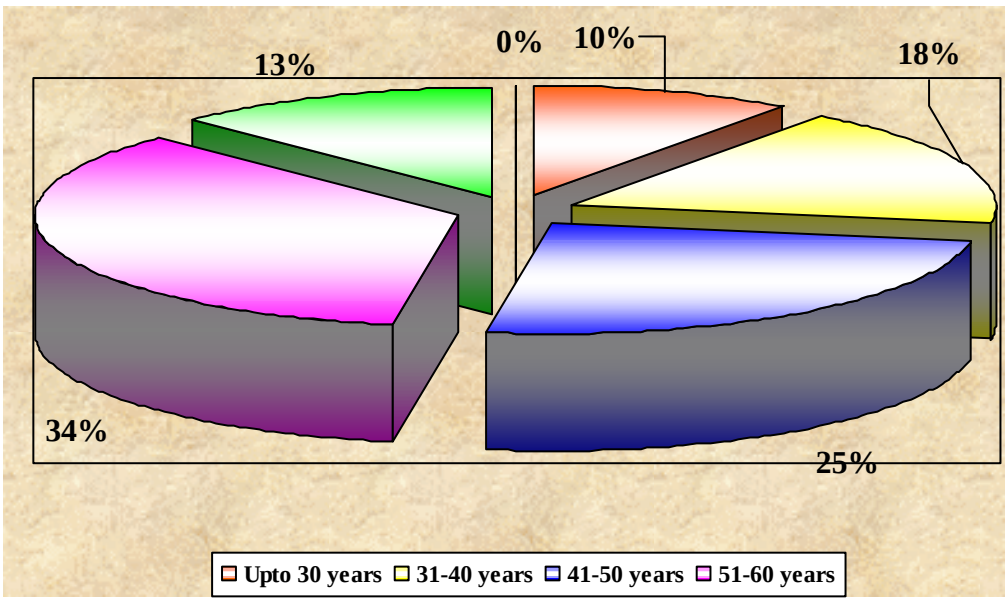

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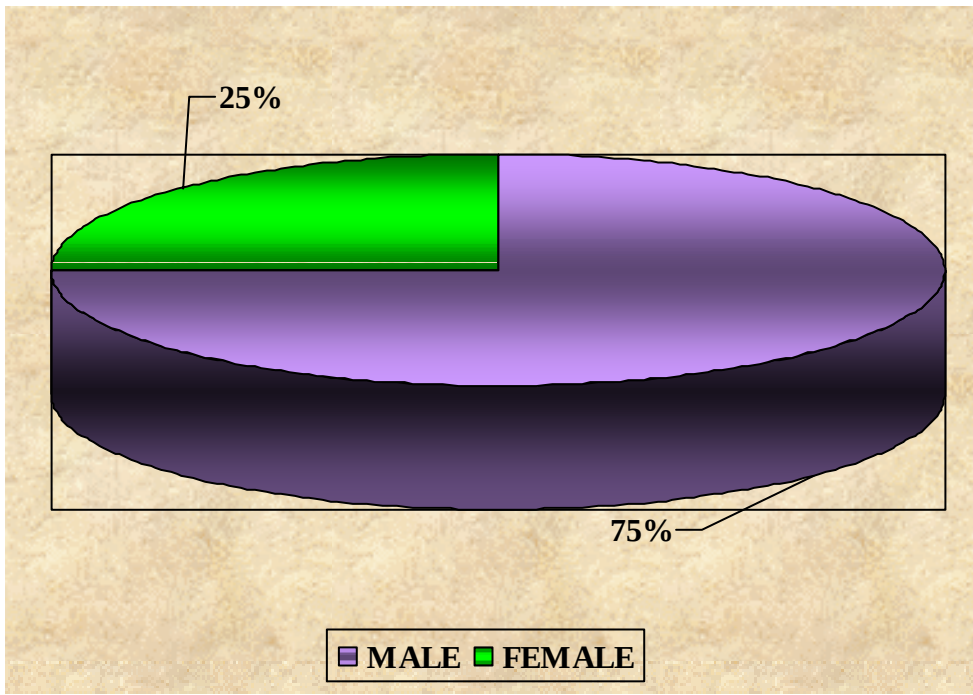

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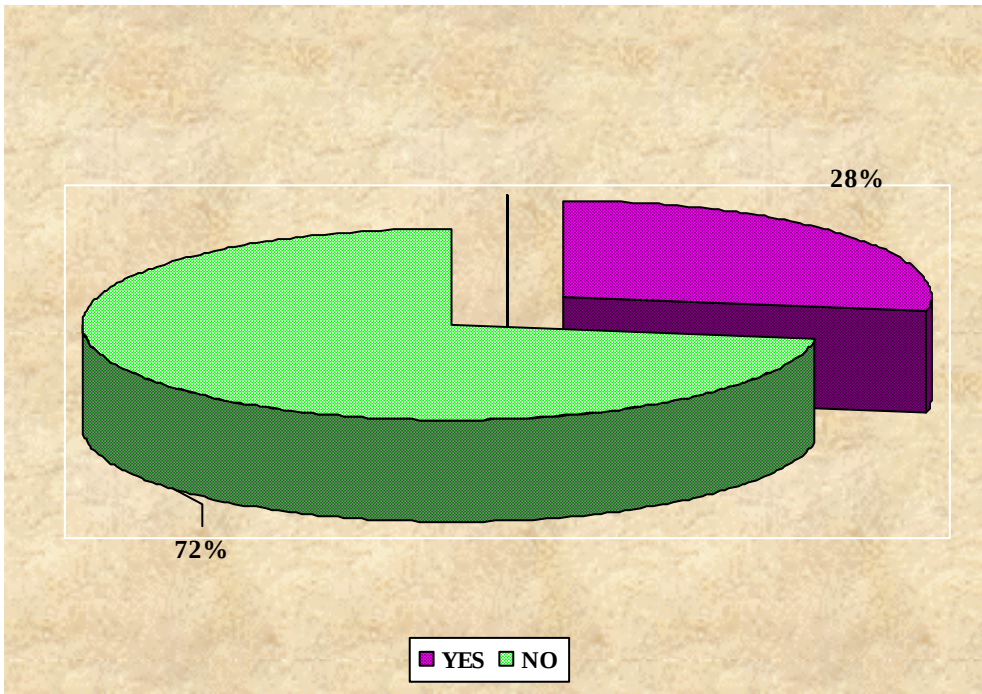

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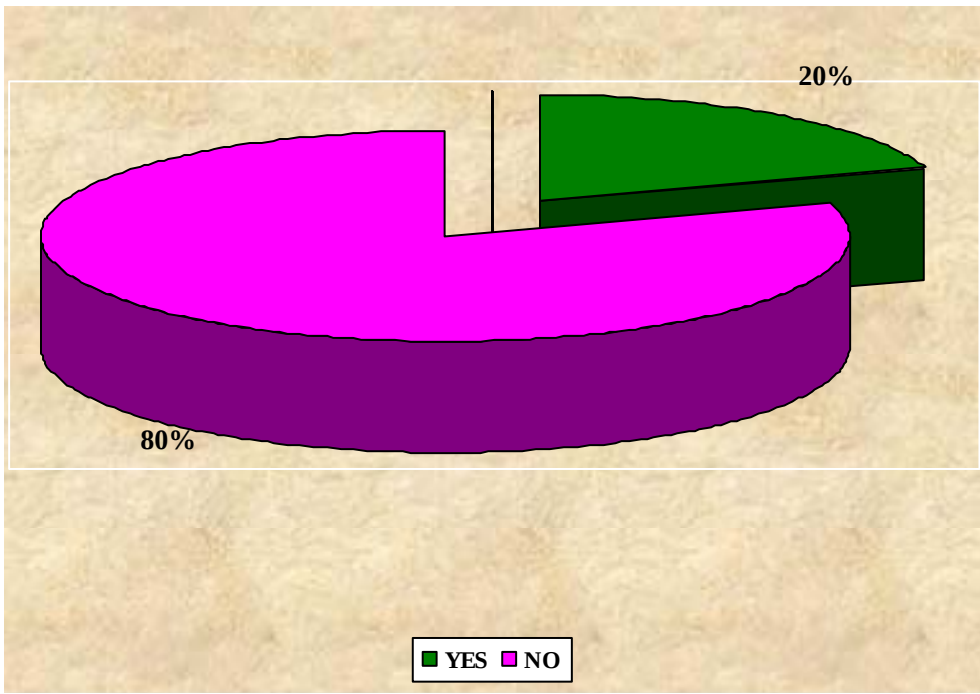
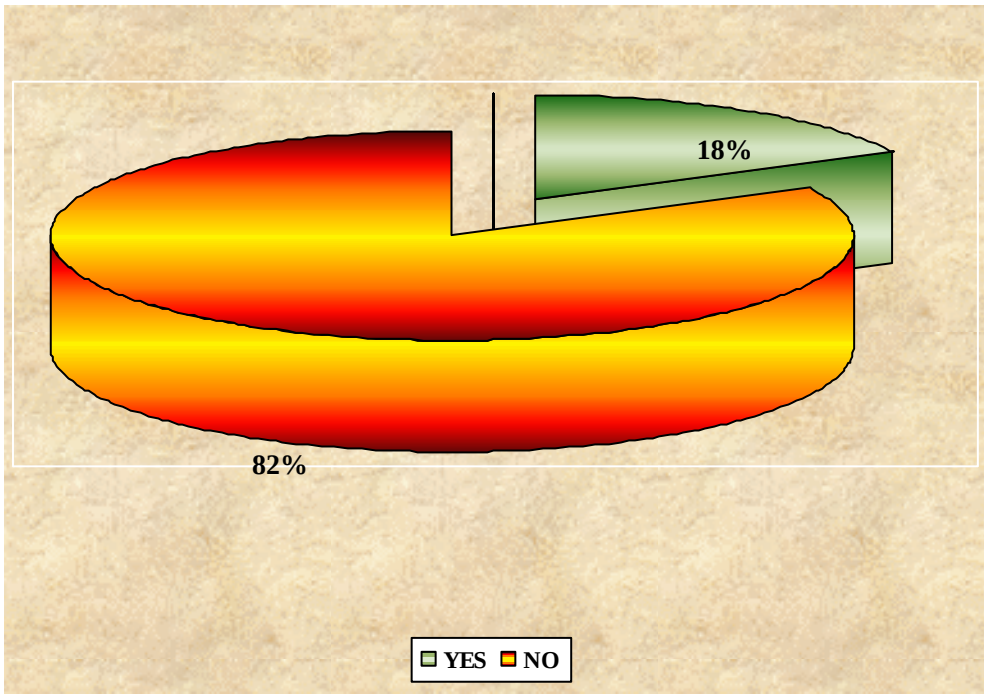


GOITRE



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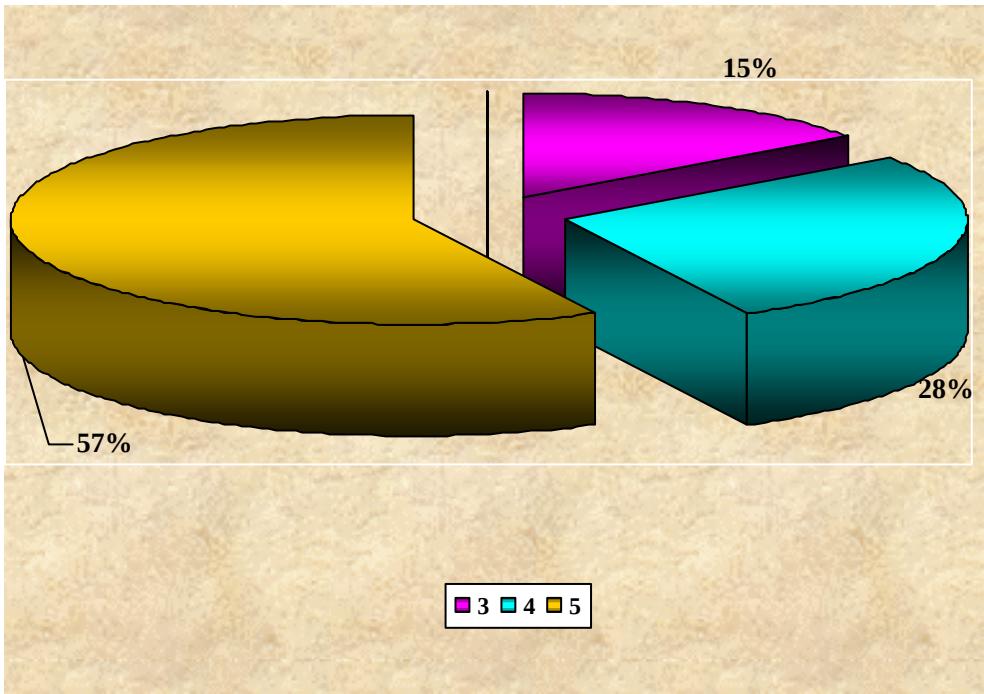
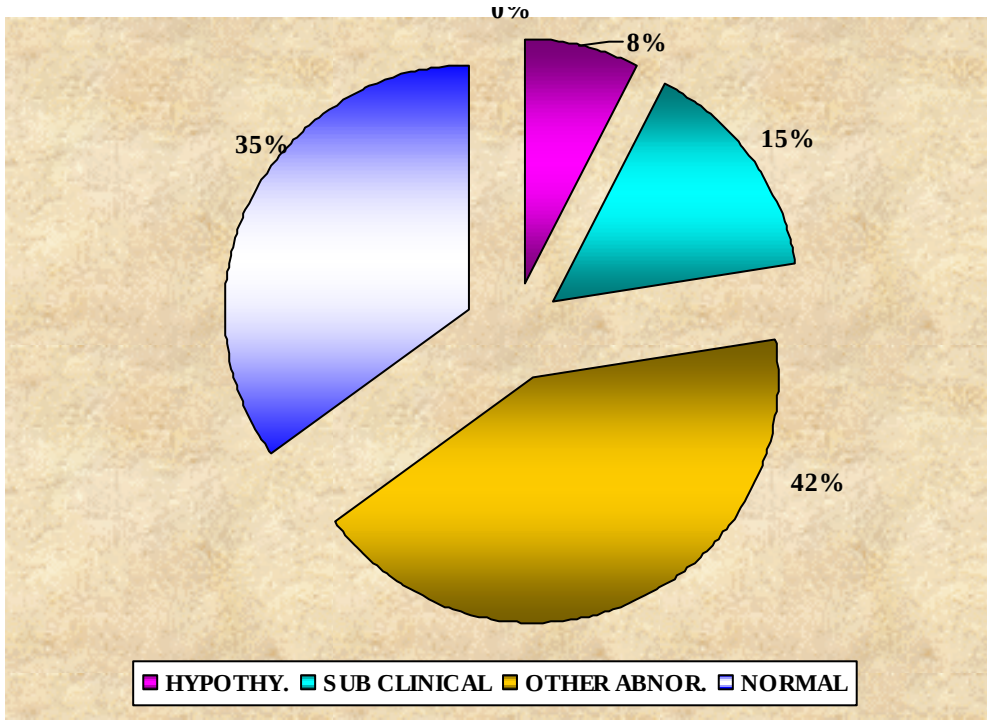
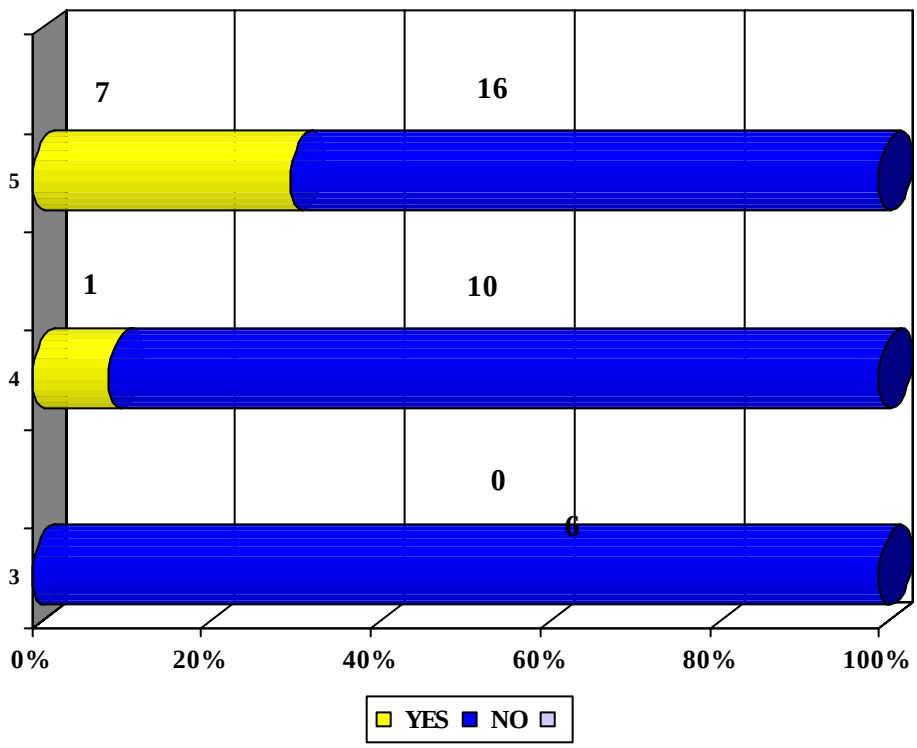


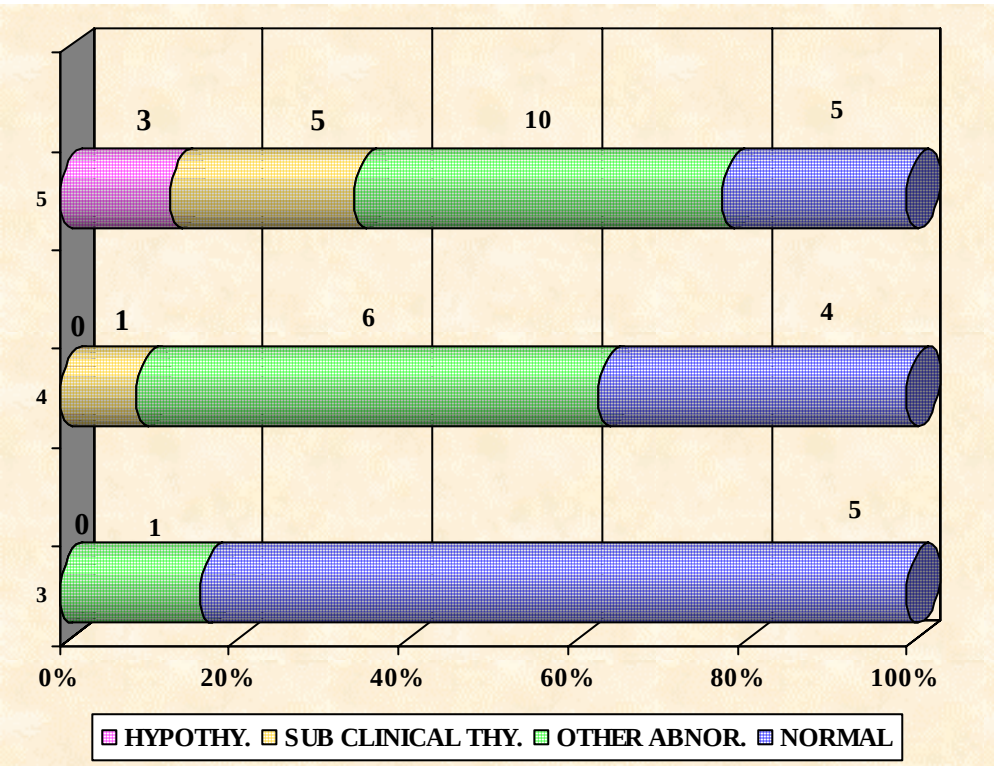
IMPRESSION



SYMPTOMS & CRF STAGE



CRF STAGE & IMPRESSIONS



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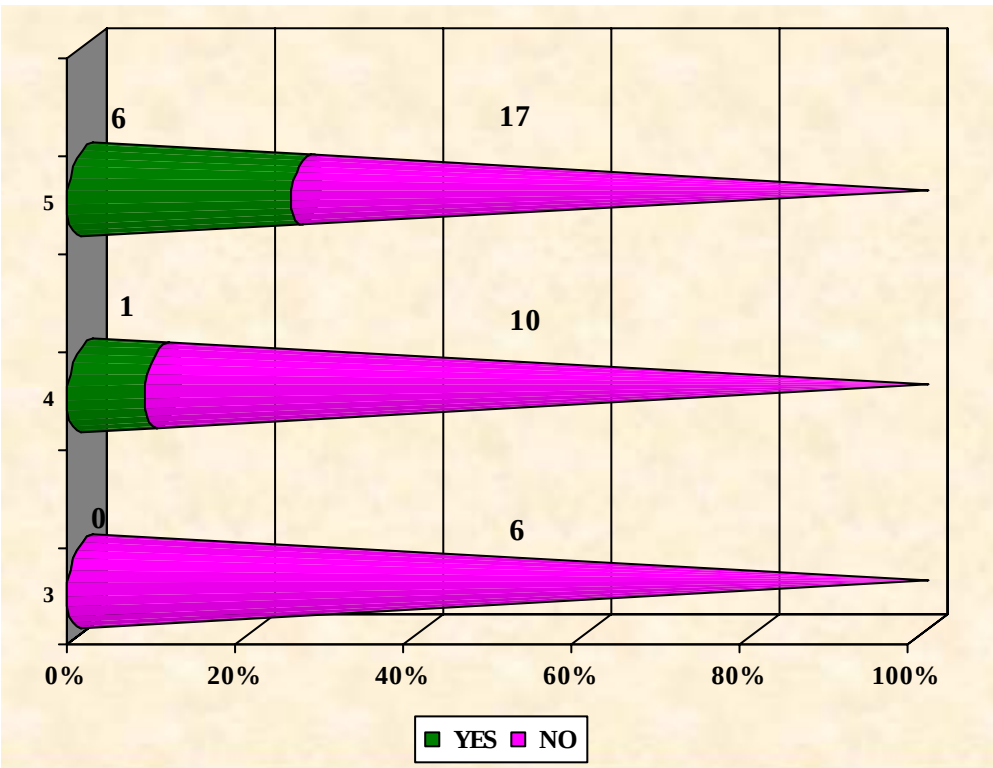
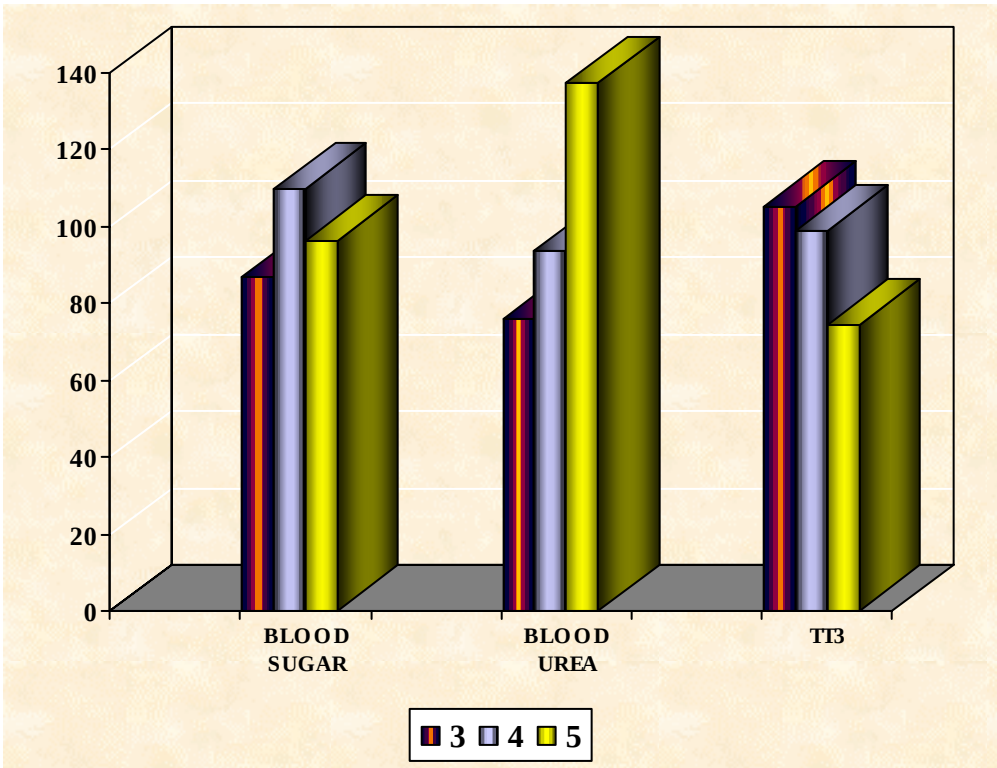


CRF STAGE &
HAEMATOLOGICAL PARAMETERS



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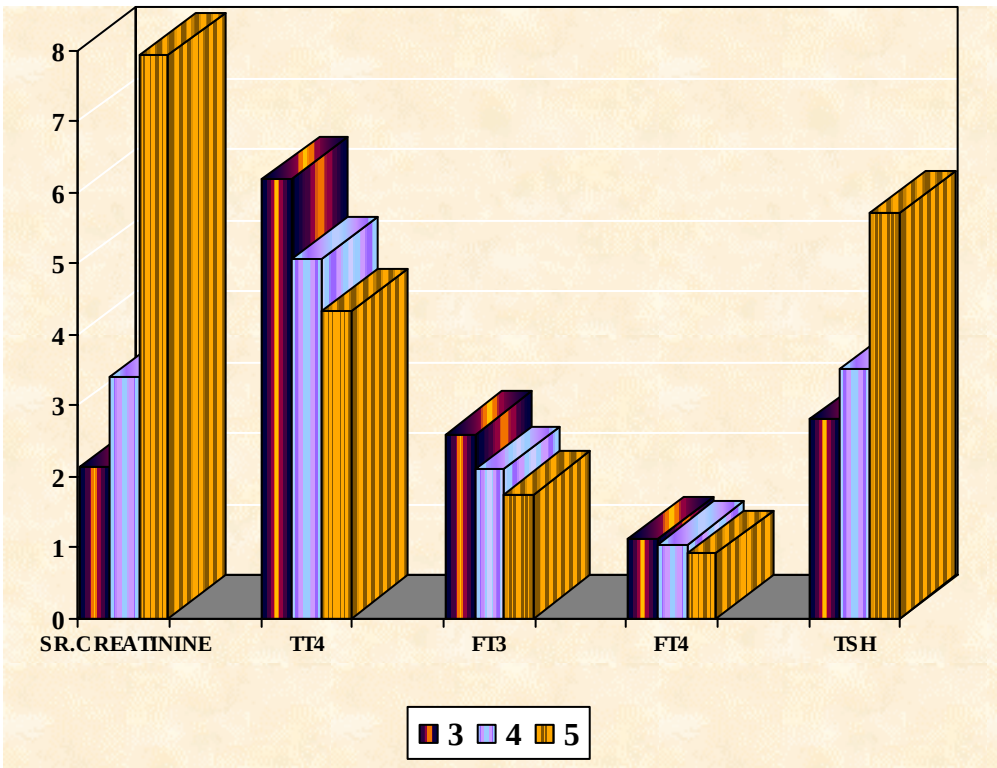
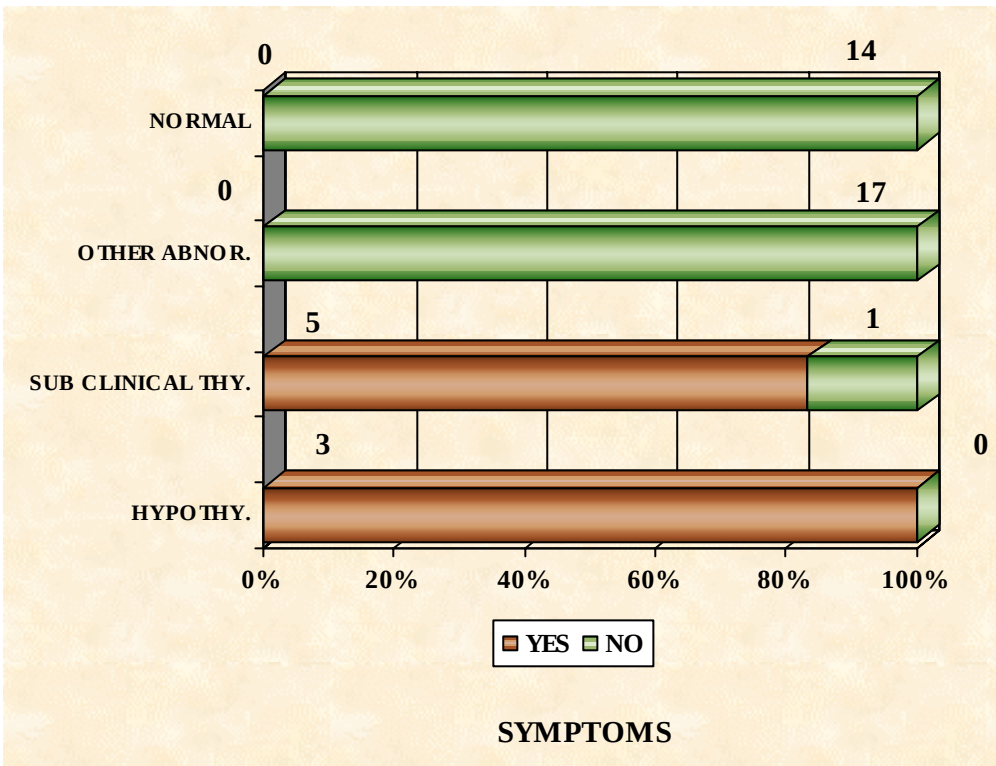
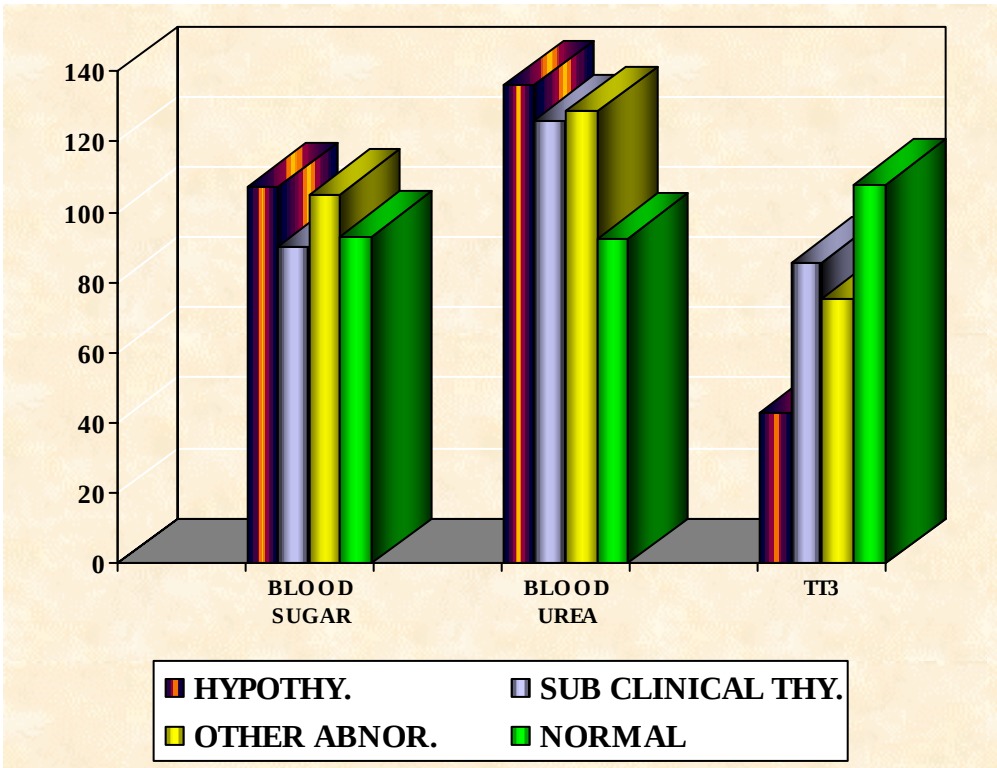


SYMPTOMS & IMPRESSIONS



IMPRESSION &
HAEMATOLOGICAL PARAMETERS



IMPRESSION &
HAEMATOLOGICAL PARAMETERS